

## FILTRATION SYSTEM FOR PREPARATION OF FLUIDS FOR MEDICAL APPLICATIONS

### Cross Reference to Related Applications

The present application claims the benefit of priority of PCT US/2005/000381 whose international filing date is 7 January 2005, which application claims the benefit of priority of PCT US/2004/000476 whose international filing date is 7 January 2004.

### Background of the Invention

Many medical applications require purified water and other fluids. for irrigation, and hemodiafiltration. Some prior art systems have focused on continuous purification processes that require a separate filtration/purification apparatuses that must be periodically purged and verified to provide sufficient constant flow of sterile replacement fluid. (See necessarily complicated and require separate pumping systems for the purification process. In addition, the rate of supply of fluid for such systems is very high, requiring expensive filters to be used. The same high-rate problem exists for the generation of replacement fluid for hemofiltration, and therefore also requires expensive filtering apparatus.

Large and small scale inline systems are known for preparation of infusible fluids and for preparation of dialysat. The following prior art references discuss examples of such systems.

US Patent Publication No. 2004/0232079 US Patent Publication No. 2003/0105435 US Patent No. 5,645, 734 US Patent No. 5,782, 762 US Patent No. 6,136, 201 PURELAB Maxima, Ultra-Pure Water Purification Systems Shipe, Brad;" The Case for UV in Applications," Water Conditioning & Purification Magazine, Jan 2003, Vol 45 No. 1.

### Brief Description of the Drawings

Fig. 1A illustrates a fluid preparation apparatus embodiment in a figurative way for discussing various features and arrangements of a medical fluid purification system.

Fig. 1 B illustrates a filter device with control elements that provide assurance of fluid quality and prevent breakthrough of contamination upon filter expiration.

Figs. 2A and 2B illustrate a filter and batch container with connector systems that ensure against contamination.

Fig. 3 illustrates a self-clamping connector.

Fig. 4 illustrates a batch container tubing set.

Fig. 5 illustrates a fluid preparation apparatus embodiment in a figurative way for discussing various features and arrangements of a water purification system.

Figs. 6, 7, and 8A illustrate portions of an embodiment of a fluid preparation apparatus.

Fig. 8B illustrates a portion of a filter module in which two redundant ultrafiltration membranes are commonly housed.

Figs. 9A and 9B illustrate embodiments of a batch container.

Fig. 10A illustrates a fluid quality sensor such as a conductivity or resistivity sensor configuration for sensing fluid quality in a container.

Fig. 10B illustrates a medicament concentrate cartridge.

Fig. 11 illustrates a filter module in partial ghost perspective view.

Fig. 12 illustrates a filter cartridge with an expansion device.

Figs. 13A and 13B illustrate fluid preparation devices for use with a replaceable filter module such as the one illustrated in Fig. 11.

Fig. 14 illustrates a control system to support features of various embodiments.

Fig. 15 is a flow chart for discussing various control options of the various embodiments discussed herein.

Fig. 16 illustrates a treatment environment for use of a control embodiment.

Figs. 17, 17A, and 18 illustrate ultrafilter configurations that are tolerant of the evolution of air from within the ultrafilter.

### Detailed Description

The present disclosure relates to apparatus, methods, devices, articles of manufacture, etc. for producing pure water and, in some embodiments, pure solutions. These may be used for the preparation of solutions for medical applications such as tissue irrigation, preparation of pharmaceutical, blood treatments such as hemofiltration, hemodialysis, hemodiafiltration and ultrafiltration, and other treatments.

As described in Figure 1A, to supply suitable water that is substantially free of unwanted dissolved and undissolved materials, a combination of permanent and replaceable components may be provided at the treatment site. Fig. is an overview of a framework that provides benefits, particularly in certain environments. One such environment is renal replacement therapy. Patients must be treated at least twice a week and often daily. On the other hand, excellent sterility design urges the use of pre-sterilized throw-away components to ensure against various modes of contamination which need not be enumerated. But replacing every component that must be contamination-free upon every use is profoundly expensive, particularly where treatments are done every day. Prior art approaches have addressed this problem by combining permanent components whose sterility is guaranteed by intensive sterilization procedures, some of which are backed up (made failsafe) by using additional disposable components that are used once and discarded. Alternatively, the disposable can be made more robust to avoid the on-site sterilization procedures. But this presents the problem of forcing the designer to use inexpensive, and therefore less desirable components in the disposable portions, or of simply imposing the burden of high cost on the medical treatment system.

Fig. 1A shows a new model that compromises on this point and is considered particularly applicable in the renal replacement therapy environment. A permanent module 920 has certain pretreatment components that may be used repeatedly without replacement and without sterilization and includes filtration and treatment steps that are not unduly inclined to aggravate, or susceptible to, contamination. Examples are illustrated in the further embodiments. This permanent module may be designed to receive variations of water quality. A semi-permanent module 922 provides more than one use, for example a month's worth of uses, but is disposable periodically or upon detection of incipient failure. The permanent module may contain a controller to enforce the proper use and handling of the semi-permanent module since safeguards must be enforced with regard to it. But with the semi-permanent modules, as discussed below in connection with particular embodiments, the procedures do not involve washing, cleansing, sterilization. The final stage includes final treatment steps provided in a single-use element in the final stage, the least expensive components may be arranged to guard against sterility failures of the upstream components. As will be seen, the preferred embodiments described herein conform to this model. Variations of the model are possible including fragmenting the intermediate modules into ones used according to other schedules such as one module replaced monthly and another replaced weekly. An example of a semi-permanent element and a control system to safeguard against contamination are shown in Fig. Note that the embodiment of Fig. 1 B may constitute an independent invention and need not be employed in a combination as discussed with reference to Fig. 1A, although this identified as a preferred configuration. Referring to Fig. 1 B, a pump, 416 feeds raw water into a filter module 425 via an input line 403. The filter module 425 contains first and second filters and embodiment, the first and second filter stages are deionizing filters. The first and second filter stages and may be accompanied by other types of filters (not shown here but discussed and illustrated elsewhere in the instant specification) in the filter module or externally thereto to perform a complete water treatment. Treated water is supplied to a batch container 417, which may or may not be present. In the illustrated configuration, water is treated for preparation of a medicament which may be included in concentrate form in the batch container 417 as a consumable unit.

Between the first and second filter stages and a water quality sensor 405 is provided. In an embodiment, the water quality sensor 405 is a conductivity or resistivity probe that detects ionic

species in the water after passing through the first stage filter preferred embodiment, the second stage 41 OB provides at least some redundancy in that the second stage 41OB provides some of the filtration effect of the first stage 41OA. In an alternative embodiment it provides all of the filtration of the first stage and is thereby completely redundant. In such an arrangement, the first stage would expire (become depleted), allowing contaminants to break through, before the second stage expires. The contaminant breakthrough is detected by a controller 415 connected to the water quality sensor 405. The controller 415 also controls the pump 416. Upon expiration of the first stage the controller allows the preparation to continue until a certain amount of fluid is collected in batch container 417, preferably an amount required for a treatment. Once this threshold quantity is delivered, the controller will not allow the pump 416 to be started until the filter module 425 is exchanged with a fresh one. The second stage filter preferably, is sized to ensure that, by itself, it can purify at least a single batch of water, plus a safety margin without any contaminant breakthrough to the output line 404. In a preferred embodiment, the second stage filter 41 OB is a smaller size than the first embodiment, the second stage filter may be of a different type which may not be as able to handle high contamination loads as the first. This may be acceptable because, although after breakthrough is detected, the emerging fluid is still substantially purified and the load input to the second stage filter may remain low until a single batch of fluid is prepared.

In an alternative embodiment, the filter module 425 is provided with a permanently attached data carrier 423 such as radio frequency identification device bar code (1-or 2-dimensional), contact-type identification device, etc. The data carrier 423 contains a unique identifier of the filter module. When a cartridge is connected to the pump, the controller 415 reads the data carrier 423 using a reader device 422 and stores the identifier in a memory 437. If the water quality sensor 405 indicates contaminant breakthrough, the controller permanently stores the identifier in an expired directory in the memory, which has a non-volatile portion for the directory. If a user attempts to connect a module 425 with an identifier stored in the directory, the controller will not operate the pump and will indicate the error condition by means of an annunciator 420 or equivalent device, such as an LCD display message.

Note that in an alternative device, the data carrier 423 is a programmable device with a writable memory. In this embodiment, the controller 415 programs the data carrier 423 with a flag

indicating that the filter module 425 is expired. The controller 415 then prevents the initiation of a new batch.

Fig. 1B also illustrates an optional embodiment with a pressure transducer 435 that may be used to test for clogging of the first stage filter 410A. When the pump 416 head pressure reaches a particular maximum, in order to allow a batch preparation to be completed, the controller activates a normally- closed valve 426 to bypass the first filter stage 41 OA. Water flows through a bypass line 427 and through the second stage filter. The expiration of the filter module 425 may then be enforced by the controller in either of the ways described above. The above embodiment may be used in filter modules 425 that contain filters that clog when depleted such as carbon filters or porous membrane filters. Not that the clogging and breakthrough devices described above may be combined or used exclusively in a given filter module embodiment. Note also that the head pressure may be sampled and stored over a period of time to determine if the pressure change profile is characteristic of a filter suffering normal usage. This would distinguish, for example, an accidental line blockage and prevent inappropriate use of the bypass line 427.

Referring to Figs. 2A and 2B, a multi-use filter device 440 has an outlet port 441 A with a cap 444A to avoid contamination. The outlet port 441 A is to a mating port 441 B, which is also capped (cap 444B). The ports 441A and 441 B may be, for example, locking connectors. A special clamping connector 442, which seals itself when disconnected from a mating connector 452 is connected to port 441 B and a line connecting it to a batch container 450 which receives purified water from the multi-use filter device 440. A microporous filter 453 guards against the introduction of contaminants by touch contamination when connectors and 441 B are mated.

The special clamping connector 442 may any suitable device that seals off, to prevent contamination. An embodiment of such a connector is shown in Fig. 3, although the sealing and disconnecting functions, to be described below, can be performed by separate mechanisms so this embodiment is not essential. An outlet tube 460 to the filter 453 of Fig. 2A is permanently affixed to a male luer fitting 478 of a male connector 452 that is received by a female luer fitting 479 of a female connector 442. The female connector 442 has a pair of latch arms 464 that engage a ridge 469 of the male connector 452. The latch arms 464 pivot on living hinges 468

affixed to the female luer fitting 479. Pinching ridges 470 and 476 compress the tube 474 when a bendable retaining ring 472 is squeezed. At the same time, engaging ends 466 of the latch arms 464 retract from the ridge 469 releasing the male luer connector 452. The bendable retaining ring 472 retains its deformed shape once it is pinched so that the tube 474 remains pinched and thereby sealed when the connectors 442 and 452 are disconnected. The bendable retaining ring 472 may be made of ductile metal, for example. The retaining ring 472 may be replaced by another suitable device such as a ratchet mechanism.

Returning to Figs. 2A and 2B, when the multi-use filter device 440 is first used, its outlet connector is sealed with a cap 444A as is the inlet connector 442 (with cap 444B) of the batch container 450. The batch container 450 may be sealed and sterilized with the special fitting 442 and its mating connector 452, which may correspond to elements 442 and 452 in Fig. 3, connected in a completely sealed and pre-sterilized state. Other ports such as a sampling port 454 may also be sealed and, if only used as outlets, protected from intrusion of fluid by means of a check valve 456 and/or another membrane filter 453 (not shown separately). The first time the batch container 450 is connected to the multi-use filter device, the caps 444A and 444B are removed and the connectors and 441 B mated. After filtered water is collected in the batch container 450, the special clamping connector 442 is disconnected and left connected to the multi-use filter device 440 to keep it sealed and free from contamination as shown in Fig. 2B. The second time the multi-use filter device 440 is used, the special clamping connector 442 is removed by means of the connector pair and 441 B and discarded while a new batch container's 450 connector 441 B is mated to the pre-existing multi-use filter device's 440 outlet connector 441A. The carries a new special clamping connector 442 and the same process can be repeated.

Fig. 4 shows an embodiment of a batch container, for example one that may be used with the foregoing embodiments, but in particular, with the above embodiments. The batch container 1 has a batch container, proper, 1, a break-off female luer lock connector 4, a y-connector, 5, a pinch clamp 6, a male 11, a non tubing clamp 13, a non-breathing cap 14 on a female luer 9. Line 15 has an in-line check valve 16, a pinch clamp 18, a break-off male luer cap 25 and female luer 19, and a female luer 21. Various tubing branches 3, 7, 10, 12, 15, 17, and 20 connect these elements. The batch container 1 is delivered to a patient treatment setting as a sealed sterile container with all terminals sealed. The batch container 1 may contain, as delivered, a

concentrate solution sufficient to create a treatment batch of fluid, such as dialysate or replacement fluid, when water is added. Concentrate may be added by means of the luer connector 21. In the tubing set delivered to the treatment site, the tubing branch 20 may be sealed and cut after the concentrate is added. Water is added at the treatment site through connection to a water source via luer 9. The water is preferably metered to provide a predefined quantity. The sterile filters should be sufficient to protect against contamination by pyrogens before water is added to the batch container 1. A sample of diluted treatment fluid may be drawn through the luer 19 before treatment. The check valve 16 prevents any contamination due to backflow from the sampling procedure. After water is added to the treatment fluid container 1, the 9 is disconnected from the male 8 and the male luer connector connected to the blood treatment system. Luer connectors are shown by way of example as are other features and these are not essential to all embodiments.

Fig. 5 illustrates another arrangement of a particular embodiment whose description follows. A pretreatment module 900 provides primary filtration from a raw water supply, for example tap water and feeds prefiltered water to a controller module 905 which provides various control functions, a pump, pressure detection and control, and permanent filtering capabilities which are not shown separately here. Water is metered by the control module into a consumable disposable module 910 which may provide deionization, adsorption filtration, microporous filtering, chemical pretreatment, etc. and any other types of filtering that may require replacement of components. The purified water is finally conveyed to the batch container circuit 915 discussed with reference to Fig. 4.

Referring to Fig. 6, pretreatment module 900 is shown in more detail. A check valve 955 prevents an air vent 953 removes air from the primary supply and a sediment filter 951 (which may be replaceable) provides substantial filtering of solids.

Referring to Fig. 7, the control module 905 is shown in greater detail. A shutoff valve 1010 is provided for safety. Pressure indicators 1015 and 1025 may be provided for monitoring the respective pressures in and out of a pump 1020. Feedback regulation may be provided to ensure that consistent metering is provided if the pump is relied upon for measuring the total quantity of water supplied to the batch container 1. A high intensity ultraviolet (UV) lamp 1031 provides a



both sterilization mechanism and a mechanism for removing chlorine and Preferably, the UV lamp 1030 is of such intensity and wavelength as to provide disintegration of a preferred embodiment, the lamp is characterized by a 245 nm wavelength and an output power of 750 up to 1500 is sufficient to remove chloramines. By oxidizing chloramines and subsequently, as described below, filtering using a deionizing filter, chloramines can be removed.

Note that pressure indicators 1015 and 1025 may be pressure transducers that feed control signals to a control device such as discussed with reference to Fig. B and to be discussed with reference to Figs. 13A and 13B.

The operation of pump 1020 may be controlled in dependence on pressure indications from such transducers. For example, if a high head pressure is indicated, an alarm may be indicated and the pump shut down. This may indicate a problem with a connected filter. Also, the pump may be operated for a short interval and a pressure decay profile recorded and compared with an expected decay profile. If the profile does not match, it could be used to indicate a leak (such as in a filter or line) or a clog in the system. If the upstream pressure goes low, it could mean that the water supply is turned off or some other fault. Each of these events may be indicated by means of an annunciator by switching off the pump to avoid damage to the system and to notify the operator to take corrective action.

Referring to Fig. 8A, the replaceable (disposable or 910 contains a first stage filter 1007 copper-zinc alloy which is used to subject the water to a reduction/oxidation process to remove ions. This removes ions through a chemical reaction. An embodiment is KDF 85 media where about one pound is used for a flow rate of 150 ml. /min water flow rate. An activated carbon filter 1005 follows which is a well-known adsorption type filter. Next three stages of strong acid cation (SAC) 1011 and strong base anion (SBA) 1009 filters follow in series. The SAC/SBA filter cartridges 1011/1009 are not mixed beds as typically used in water filtration applications. They separate the cation and anion stages as illustrated because it has been determined to be much more effective at removing colloidal aluminum from the treated water. Note that the order of the SCA and SBA beds is not limited to what is shown and that they can be housed in a single canister or multiple canisters. Also note that other components can be sequenced differently as well as should be clear from this disclosure. For example, it should be clear that the pump 1020

can be used in a pushing arrangement to draw water through the UV lamp and the particulars of the arrangement are not limiting to the inventions disclosed. Also note that the resistivity probe 1022 can be included within a single deionizing filter between previous and following deionization stages and employed to similar effect. In such an embodiment, a deionizing filter would have leads or contacts to connect the probe to an external measurement device or controller.

Note that instead of using layered beds in a single cartridge as described, separate cartridges each containing one of a SBA and SAC filter bed may be used. Also, each cartridge could contain more than one layer of each to provide similar results.

The resistivity probe 1022 detects ion concentration by contact testing of the resistivity of the water. A signal is generated to indicate that this will be the last allowed batch before the system will require the replacement of the replaceable module 910. Control may be provided as in the embodiment of Fig. 1 B, discussed above. The second filter in the present embodiment, which backs up the first stage suffering from breakthrough, is a mixed bed deionization filter 1031. This ensures that the current batch can be completed. A second, final safeguard resistivity or conductivity test is provided with an audible alarm at 1025 as a back up safety measure. If the value it detects is above a certain level, the pump 1020 may be shut off and an alarm sounded. This may come into play if the resistivity probe 1022 fails, or if the safeguards discussed with reference to Fig. 1 B are breached. TP is a hydrophobic membrane air vent which allows air in 1035A and 1035B to be purged. The 1035A and 1035B may be a filter such as used for dialysis. An air vent may also be provided as shown at 1047. The air vent may, for example, have a 1.2 micron hydrophilic membrane that blocks air. There is a hydrophobic membrane port which allows air to vent from the filter. These are available as off the shelf components. Any suitable air elimination device may be used and these features are non-limiting of the described embodiments. Also, the second stage MBDI type filter 1031 can be a layered deionization filter such as 1002C with the same benefits as described in terms of providing protection against breakthrough. Also, the final resistivity sensor 1025 can be located as shown or moved to another location downstream of the final deionization stage, such as after or between the 1035A and 1035B, and the configuration shown is not limiting of the invention.

Note, it should be clear that resistivity probe 1022 may be used in a configuration such as that of Fig. 1 B, with the resistivity probe 1022 corresponding to sensor 405 such that filter module 910 corresponds to filter module 425.

Note that two separately-housed ultrafilters 1035A and 1035B are serially interconnected. The separate housings ensure against failure mechanisms such as grow-through of pathogens, adjacent simultaneous or shared seal failure. For example, prior art reference US Patent Publication No. 2004/0105435, cited in the Background section, shows a filter cartridge with two microporous membranes in adjacent layers of a filter cartridge housing. These may share a seal mechanism or adjacent seals such that failure of the seal of one necessarily involves failure of the seal of the other. Also, once a grow through problem occurs in one, the adjacency may cause the problem to creep directly into the adjacent membrane. These problems are prevented by the illustrated arrangement of separate redundant

Note that the benefit of separately housed filters may be substantially provided in a single housing by substantially separating two ultrafilter layers. Referring to Fig. 8B, for example, a multilayer filter with various types of filter elements housed in a common cartridge 1052 contains two ultrafilter layers 1050A and 1050B. The cartridge may be as described in US Patent Publication No. 2004/0105435, which is hereby incorporated by reference as if fully set forth in its entirety herein. The two ultrafilter layers 1050A and 1050B, separate membranes, are kept apart by an intermediate layer 1056, which may be a spacer or another filter medium. Separate seals 1057A and 1057B, which are also spaced apart, are provided.

Note the final 1025 may control the pump, as noted. A controller 1090 may be to the disposable filter module 910 and configured to stop the pump 1020. The trigger resistivity safety level to cut-off the pump 1020 may be 1 megohm, but may be raised to 2 megohm to allow the use of required temperature compensated resistivity probes (an FDA & AAMI requirement) This does allow use of low cost in-line resistivity probes in the disposable filter module 910.

Preferably, the filter module 910 as well as the modules of other embodiments is of such a flow rate that upward flow of fluids is possible.

Generally, prior art deionization beds suffer from the problem of floating or loosening resin particles which may have been disturbed during handling. The separation and floating of the particles breaks up the beds and renders the filters less effective. To avoid this, generally, filter systems are configured to direct flow downwardly through the beds to help keep and compress the resin particles.

But if flow rates are kept low, as may be done in the present system, water may be flowed in an upward direction which helps to eliminate air from stream. Air is a notorious problem in the preparation of medicaments such as dialysat. The precise flow rates needed to allow upward flow will vary according to the characteristics of the system. One way to allow faster flow rates without being hampered by break away resin particles is to provide a bed compressor of resilient porous material to compress the bed. Referring momentarily to Fig. 12, in a filter cartridge 1150, a resilient compression layer 1140 urges the filtration material 1145 in a downward direction. The resilient compression layer may be any suitable polymeric or rubber like material that is compatible with the application.

The following is an example procedure for using the devices discussed with reference to Fig. 4.

1. Remove the dialysat concentrate tubing set 915 and remove the cap 14 from the tubing line 7 that contains the filter 11. (The 0.22 micron filter 11 provides additional protection from inadvertent contamination.)
2. Connect the outlet line 404 to the concentrate bag luer connection 9.
3. Break the frangible luer connector 4 which connector is configured to form a permanent seal on the side facing the Y-junction 5 when disconnected.
4. Add predetermined quantity of water into the concentrate bag using the purification plant through tubing branch 7 through connector 9.
5. Optionally a user can write on the bag label the date and time water was first added to the concentrate bag, to assist in ensuring that it is used within a period of time. An automated scheme may be employed as well.
6. Shake the batch container 1 well to mix.

7. Confirm solution conductivity prior to use. Remove the break-off cap 1 and draw sample from this branch 15. After removing the sample, clamp the line using the pinch clamp 17 provided.

8. (The following is normative according to a preferred embodiment and not limiting of the invention) Conductivity must be in the range 13.0 to 14.4 mS/cm. Nominal conductivity for the dialysat solution is 13.7 mS/cm. If conductivity does not meet this specification do not use it. Verify that the results are accurate. If conductivity is high additional water may be added to bring it within specification. If conductivity is low then the solution must be discarded.

9. Using the non re-opening clamp 13 provided, clamp the line that is connected to the water purification plant.

10. The clamp 6 is, next, clamped on the line that is connected to the dialysat bag 1.

11. Disconnect the water source at the luer connection 26.

12. Connect the bag of dialysat solution to the dialysis circuit at the connection 8. This leaves the filter 11 and permanent clamp 13 in place to protect the water supply source.

13. Unclamp the line going to the dialysat bag using clamp 6, and initiate treatment after verifying that dialysate will be used within 24 hours from when water was added.

Referring to Figs. 9A and a batch container 100 has a fluid quality sensor 135 of a probe 120, such as a contact-type conductivity sensor.

The latter may simply be two metallic surfaces separated by a known distance and of a given area that has been calibrated. A cage 135 in a support 105 sealed to the wall 130 of the batch container 100 which may be a polymer bag as typically used in the medical industry. The cage 135 prevents an opposing wall (not shown separately) from preventing fluid from circulating around and through the cage and in contact with the probe such that a reading of the probe 120 is improved. The probe 120 extends from the support 105 and has a lead 122 with a signal connector 125 that can be connected to a controller (discussed later). The probe 120 is an independent element and can be used with any of the embodiments so its description here in

combination with other features is not intended to be limiting. Note that preferably, the probe assembly is permanently sealed to the batch container such that there is no possibility that contaminants can enter the batch container 100 interior.

At 110, a fitting connecting a sample or feed line 145 is shown. The latter may be used, with a connector 156, connect a sampling syringe to draw out a sample of a medicament or infusate. A check valve may be provided at 155 to prevent ingress of contaminants. A clamp (not shown separately) may be provided as well to guard against contamination. In an alternative embodiment, line 145 may be configured for injecting a soluble concentrate into the batch container 100 before the container 100 is sealed and sterilized as a unit (for example, by gamma ray sterilization). When a prescribed quantity of purified water is added to the batch container, the diluted concentrate may form a medicament or infusate such as replacement fluid for hemofiltration or a dialysat for hemodialysis. Line 145 may also represent a draw line that may be connected to a treatment machine. In the latter case, a sterile filter (at 155), such as a microporous membrane of 0 be provided to guard against touch contamination. Additionally, a clamp may be provided as at 155.

In the embodiment of Fig. 9A, purified water may be added to the batch container by another instance of a line similar to 145. Alternatively, if concentrate or other medical solute or medication is contained in a separate container, such may be added to the batch container 100 by means of a double lumen spike 174. (Details of a suitable dual lumen spike can be found in US Patent Publication No. 2004/0222139, which is hereby incorporated by reference as if set for in its entirety herein). A spikable bag 170 contains, for example, medical fluid concentrate such as concentrated dialysat. Purified water is pumped through connector 182 of line 180 and passed into the bag (after spiking) by the dual lumen spike 174. The fluid circulates in the bag carrying its contents back through the dual lumen spike 174 through line 172, through a filter 150 into the batch container. The dual lumen spike may be sealed by means of a removable cap 175 so that the batch container and fluid lines can be sealed and sterilized and later delivered as a unit without contamination. Clamps 157 may be provided to seal the batch container 100. A special clamping connector 442 may be provided and used as discussed with reference to Fig. 1 B in line 100. If concentrate is present in the batch container 100 rather than using a spiking bag 170, the

concentrate may be used to obtain a data point for a calibration line fit for measuring fluid conductivity.

Referring to Fig. 9B, instead of providing a conductivity or resistivity sensor in the batch container 100, a dual lumen takeoff 255 with a common lumen (Y-configuration) 260 housing a water quality sensor 262 of a probe 210 with corresponding signal connector 220 and lead 215. A syringe port 240 and check valve 242 are connected inline to the other branch of the Y-junction.

When a syringe (not shown) is attached and fluid drawn into it, fluid from the batch container passes over the water quality sensor to allow its quality to be measured. In other respects the elements of Fig. 9B are the same (and identically numbered) as those in Fig. 9A.

Referring to Fig. 11, a replaceable multiple use filter module 1125 as may be used in the various embodiments described herein has an inlet port 1130 and an outlet port 1110. A physical arrangement of filter cartridges is shown which provides for a compact module 1125 that is advantageous for packaging and assembling to a chassis (as discussed relative to Figs. 13A and 13B). Tubing 1116 runs from the top of each cartridge 1111 to the bottom to provide upward flow as discussed earlier. A signal port 1100 for reading fluid quality sensors 1115 and 1105 is provided in a housing. 1127. Signal port 1100 may have a lead wire and connector installed to it or one may be provided separately. Alternatively, signal port 1100 may be a wireless port powered by a battery. Signal port 1100 may include a data carrier as discussed with reference to Fig. B or a data carrier may be provided separately or without the signal port if a fluid quality sensor is not provided.

A data carrier may include software and instructions for using the filter module 1125. These may be read by a permanent component of a filtering system as described in connection with Figs. 13A and 13B. A base unit 335 may be configured substantially as described with reference to Fig. 5 with the base unit 335 housing the components of the permanent pretreatment module 900 and controller module base unit may contain a display 330, such as an LCD display. Instead of, or in addition to, a display, the base unit (and other embodiments described herein) may have a voice generator or other type of output device. An inlet port 341 may be provided for receiving

raw water to be filtered and an outlet port 340 for attachment to a filter module (which may be multi-or single-use) which is received in a locating station 315. The latter may have a reader 311 to read a data carrier or to connect with a fluid quality probe such as one or more conductivity sensors described above. A further locating station may be provided such as 305 for a batch container. This may have a data carrier reader 320 and/or various other components (at 321) such as a heater, a mixer, such as a moving field generator for magnetohydrodynamic mixing of the contents of an installed batch container. The base unit 335 may have a port 310 for connection to a fluid quality probe of the batch container. This may provide a calibration input as well as a final measurement of fluid quality. The embodiment of Fig. 13B additionally provides a locating station for a concentrate container such as 170 described with reference to Figs. 9A and 9B. The base unit 335 may further be fitted with a controller containing a computer with a connection to the Internet or other network connecting the base unit with a server 390.

In an embodiment, features indicated at 301-306 may be added to allow the base unit 335 to control when and whether an outlet line of a batch container should be opened and clamped. A batch container is fitted in the station 305 and an outlet line of the batch container fitted between clamping portions 303 and 304. A detector 306 verifies that the line has been fitted in place. When the system is run, an actuator 302 and motor 301 may be activated to clamp the line during fluid purification and as the batch container is filled.

After the batch is filled, the clamp may remain closed until a treatment operation, which may be run while the batch container remains in place, is begun. At treatment time, the clamp mechanism 303 and 304 can enforce the expiration time of the batch of fluid. For example, a timer can be started within the controller of the base unit or, equivalently, a time/date stamp stored and the clamp only released if the batch of fluid is used for treatment within a certain period of time. For this purpose a treatment machine and the base unit 335 may be combined into a single device under common control or the two may be linked by a data link to operate cooperatively to achieve such a result. The flow chart of Fig. 15 describes the control steps involved.

Referring now to Figs. 9A and instead of a concentrate container in the form a spikable bag 170 as illustrated in connection with Figs. 9A and 9B, a cartridge 271 as illustrated in Fig. 10B may



be used. Here, concentrate 280 is within a sealed cylinder 274 with a piston 273 and a burstable seal membrane 275. The cartridge may be fitted in the base unit 335 (Figs. 13A and 13B) which may contain a linear drive 270 and plunger 272 to push the piston 273 thereby bursting the seal membrane 275 and inject contents into a T- junction 278 in the path of purified water sent into the batch container 100. Note that the cartridge 271 may be provided as part of the sterile batch container fluid circuit shown in Fig. 9B.

Referring to Figs. 14 and 15, the base unit 335 and corresponding parts of other embodiments described herein may contain a programmable controller including an embedded computer 600 with memory, non-volatile storage, communication elements, etc. Various sensors 605 such as discussed in connection with various embodiments may be connected to provide input to the controller executing a program stored in memory. The latter may be stored in firmware or obtained from a data carrier via a data port 610 as described previously. In addition, a network or Internet connection to a server 625 may be provided to obtain and transmit data such as software, instructions for use, expired identification codes, etc. Actuators 615 such as valve clamps, pumps, and annunciators 620 such as alarms may be provided as well.

A sample program for operating the various embodiments described herein is shown in Fig. 15. The process may begin with firmware until software loaded at a later stage takes over. Software may be read from a data port or data store and instructions for using the system output at step S5 whereupon the system waits for user input. The instructions may indicate to press hard or soft key to continue at which point steps S10 and S15 are executed to determine if a no-go condition exists. If a necessary component has not been connected, step S30 will be executed and the system may output an appropriate message to instruct the user to take corrective action and wait for response. Similarly, if in step S15, it is determined that a component is expired, such as a batch bag that has been previously used or a filter module has been used and previously indicated as having suffered breakthrough, step S30 will be executed. At step S20, various system tests may be performed such as a pressure profile test or quality test. Tests may also include determining if the conductivity indicated by a connected conductivity probe is within specified limits. In step S25 it is determined if all tests have been passed and control passes to step S35 where fluid preparation is begun. If not, step S 30 is performed and appropriate output is generated on a display such as 330. If a value goes out of range at step control passes to step S60

to determine if an expiration event has occurred, for example, breakthrough of contaminants in a filter module. Note that Filter modules may be "stamped" with a permitted time of use after a first use when presumably the seal was first broken. This may be enforced in the same manner as discussed with reference to attempted reuse of a filter module after breakthrough was detected. Thus, step such an event may be detected at step S60 as well.

At step S55 depending on the type of data carrier (e. g., programmable or just carrying a unique the expired or spent unit is indicated as expired so that reuse can be prevented. For example, in S55 the data carrier may be programmed with a token to indicate that the attached filter module is expired or a server may be sent a message to indicate that its unique ID should be added to a list of expired IDs. Any suitable device may be used to "expire" a unit. Since expiring a unit may still allow a batch to be prepared, control returns to S40. Completion of the treatment may be determined at step S45 by measuring the total mass pumped or by other means. For example, if the embodiment provides a conductivity probe in the batch container, step S45 may depend on the measured conductivity of the batch contents. Once completion is determined, the system may be halted at step S50 and the batch bag "stamped" with a time and date. Note that further instructions may be output at this point.

In one embodiment, the water purification and treatment may be done from a single apparatus and under common control. The steps following step S50 illustrate this. Assuming purified fluid has been added to a batch container of some description such as those described in the current specification or some other, the contents of the container may be mixed, if a solute is involved, and the contents checked in some way in step S51. For example, the conductivity of a mixed batch or the resistivity of a pure batch can be checked determine its conformity with treatment specifications. In step S52, if a value is out of range, control passes to step S30, but if not, the batch may be utilized at any time up to an expiration time/date (MTU time, or Mixed Till Use-time). In step S53, an outlet clamp that prevents fluid from being drawn from the batch container is released to allow a treatment to be performed with the fluid product. At the same time, an acceptance message can be output to the user on a display. At this time, in S54, a time stamp is stored or a timer started to keep track of the expiration of the batch of fluid. If the expiration is not observed, which is tested at step S56 by checking to see if the timer has expired, the clamp will close in step S30 (under the general step indicated as "take action") and an appropriate

message output. The system will then wait until treatment is completed while, optionally, continuously checking the MTU timer in steps S46 and S56.

Note that many of the described mechanical and control features are novel and inventive alone, as subcombinations with other features and their description in combination in the above embodiments is not intended to be interpreted as limiting of the inventions disclosed herein. Referring to Fig. 16, when a treatment machine 700 attempts to use a batch container 710 tagged with an expiration date at step S50, it can determine if the date has passed and prevent use of an expired batch container thereafter. This may be implemented with contact or wireless data reading devices, a programmed smart card type device or via an Internet server as described with reference to the mechanism for enforcing non-reuse of filter modules.

Referring to Fig 17, air may evolve from fluid as it passes through an ultrafilter 714. Preferably, the ultrafilter 714 has a high membrane surface and in such filters, the potential for air evolution may be fairly high. To avoid problems with bubbles forming in the filter, the embodiment of Fig. 8A shows transducer protectors TP, which are hydrophobic air vents. But the lines leading to them can fill with water and render them useless for air purging. A refinement of the configuration of Fig. 8A, which may be used in any water treatment plant as a final protective stage, is to provide an ultrafilter 714 (which may be a standard dialyzer capped at the lower blood port) with an inlet 712 and outlet 704 on one side of the membrane connected by a return line 704 flowing through an air filter/vent 706, through further line 708 into a T-junction 717 and back into the inlet line 712, fluid is drawn out through line 707. Again, the filter/vent 706 may be a 1.2 micron air vent with a 1.2 micron hydrophilic membrane that blocks air and a hydrophobic membrane port which allows air to vent from the filter. These are available as off the shelf components. The water column defined by line 708 is denser than the corresponding column within the housing of ultrafilter 714 so that a return flow will exist through the branch 704, 706, 708. The reason for the lower density is due to the evolution of air in the ultrafilter 714.

An alternative design that integrates air vent configurations into the housing of the ultrafilter 714 is shown in Fig. 17A. For the outlet (filtrate) side of integrated into the outlet of an ultrafilter 715 and an air filter such as a hydrophilic air filter membrane 766 integrated into the outlet. Any bubbles coming out of fluid collect at the top of the filtrate side (in a header space of a

membrane type filter) and be vented by the hydrophobic air vent 765. On the inlet side of the ultrafilter 715 (the side of the filter media that has not yet been ultrafiltered), air collecting in the inlet side will leave by an air vent 467, for example one using a hydrophobic membrane 469. A check valve 742 may be provided to prevent siphoning and/or reduce risk of contamination.

Referring to Fig. 18, to address any problem with inadequate flow through the return branch of the Fig. 17 embodiment, a resilient channel element 730 such as an inline bladder 731 may be included with check valves 724 and 728. When the system pumps fluid, the resilient channel element 730 stores fluid under pressure and releases it in pumping fashion when the system stops pumping. Again, an air filter/vent 724 allows air to escape and purged from the return line 726. The return flow problem can also be dealt with by replacing the T-junction 717 with a Venturi device configured to create a suction in line 708 by using an accelerated fluid flow through the line 714,712.

One of the drivers for the features discussed above is a need to provide pure water irrespective of input water quality. The above embodiments are not reliant upon water quality and are designed to reliably produce pure water or solutions regardless of input water quality. Various embodiments are also designed to reduce the costs associated with lower volume (10-60 liters) preparation of medical and other pure solutions and to maintain simplicity through the combination of semi-permanent and single-use modules which combine to eliminate the complexities, costs and safety issues associated with maintenance, sterilization, and operation of many other prior art systems.

Although the foregoing inventions have, for the purposes of clarity and understanding, been described in some detail by way of illustration and example, it will be obvious that certain changes and modifications may be practiced that will still fall within the scope of the appended claims. For example, the devices and methods of each embodiment can be combined with or used in any of the other embodiments. For another example, the air vents described can be of any suitable description and need not be membrane type air vents at all, although these are preferred.

## ABSTRACT

Systems, methods, and devices for preparation of water for various uses including blood treatment are described. In embodiments, fluid is passed either by pump or passively by gravity feed, through various filtration elements from a fluid source to a treatment fluid container. The latter forms a batch that may be used during treatment. The advantage of forming the batch before treatment is that the rate of filtering needn't match the rate of consumption during treatment which provides multiple benefits and liabilities to overcome, as discussed herein. Mechanisms for preparing pure water for infusion or medicaments are described such as elimination of chlorine and colloidal aluminum. Also various control mechanisms to help avoid contamination are described.

## CLAIMS

1. A controller device for a water treatment plant, comprising:  
a controller adapted to read a unique identifier of a connected filter and a fluid quality sensor reading;  
a pump;  
said controller being configured to continue pumping if, during a pumping operation, said fluid quality sensor gives a first indication indicating that said filter module is performing adequately;  
said controller being configured to continue pumping until a predetermined quantity of fluid has been pumped if, during a pumping operation, said fluid quality sensor gives a second indication indicating that said filter module will fail imminently, but thereafter to not pump fluid if a same unique identifier is read as when said second indication was received by it or by another similar controller.
2. A controller as in claim 1, wherein said controller includes a data carrier reader to read said unique identifier stored in said data carrier attached to said module.
3. A controller as in claim 1, wherein said controller is configured to not pump fluid if a same unique identifier is read as when said second indication was received by it or by another similar controller by comparing a read identifier with a stored identifier in said controller or one read by said controller from a database of unique identifiers.
4. A controller device for a water treatment plant, comprising:  
a controller adapted to read a unique identifier of a connected filter and a fluid quality sensor reading;  
said controller adapted to read a water quality from a fluid quality sensor;  
said controller being configured to continue generating pure water using a filter module when said fluid quality sensor gives a first indication indicating that said filter module is performing adequately;  
said controller being configured to continue generating water until a predetermined quantity of fluid has been pumped if, during a generating operation, said fluid quality sensor gives a second indication indicating that said filter module will fail imminently, and thereafter to halt pumping until said filter module is exchanged.

5. A controller as in claim 1, wherein said controller includes a data carrier reader to read said unique identifier stored in said data carrier attached to said module.

6. A controller as in claim 1, wherein said controller is configured to not pump fluid if a same unique identifier is read as when said second indication was received by it or by another similar controller by comparing a read identifier with a stored identifier in said controller or one read by said controller from a database of unique identifiers.

7. A controller device for a water treatment plant, comprising:  
a controller adapted to read a unique identifier of a connected filter and a fluid quality sensor reading;  
a pump;  
said controller being configured to continue purifying water during a purifying operation with said filter module when said fluid quality sensor gives a first indication indicating that said filter module is performing adequately;

said controller being configured to continue purifying water with said filter module until a predetermined quantity of fluid has been pumped if, during the purifying operation, said fluid quality sensor gives a second indication indicating that said filter module will fail imminently;

said controller being configured to either record an identifier read from said filter module in a list of used filter modules or program said data carrier thereof with a token indicating that said filter module is used; in either case, thereafter to not pump fluid if the same filter module's data carrier is later read by said controller such that a reuse of said filter module is prevented.

8. A water treatment plant comprising:  
a filter module including first and second filters connected in series and connectable to a supply of fluid;  
a pump;  
a controller with a fluid quality sensor connected thereto;  
said fluid quality sensor being connected to detect a quality of fluid between said first and second filters;  
a filter module detector connected to said controller configured to uniquely detect a filter module connected to said pump;  
said controller being connected to control said pump responsively to a signal from said fluid quality sensor and said module detector;

said controller being configured to continue pumping if, during a pumping operation, said fluid quality sensor gives a first indication;

said controller being configured to continue pumping until a predetermined quantity of fluid has been pumped if, during a pumping operation, said fluid quality sensor gives a second indication, but thereafter to not pump fluid until said filter module is replaced with a different one not corresponding to said unique one.

9. A plant as in claim 8, wherein said first and second filters are deionizing filters and said fluid quality sensor is a conductivity sensor.

10. A plant as in claim 8 wherein said filter module detector is a reader for a data carrier.

11. A water purification plant for preparing treatment fluid for use in extracorporeal blood treatment, comprising:

a resistivity monitor that is configured to shut a pump down when resistivity falls below a predetermined conductivity;

a filter including first and second deionization stages;

said resistivity monitor being positioned to detect a water quality between said first and second deionization stages, the first stage having a larger capacity than said second stage;

whereby, when said a controller may detect low a resistivity and thereby break through of contaminants and consequent need for replacement of said first and second deionizing stages while said second stage is able to continue to filter thereby providing continued filtration for a time after break through of said first stage.

12. A plant as in claim 11, wherein said predetermined conductivity is about 2 megohms.

13. A water purification plant for preparing treatment fluid for use in extracorporeal blood treatment, comprising:

a replaceable deionizing filter module including a deionizing filter having first and second filter portions, configured such that water to be filtered flows first through said first portion and then through said second portion;

a resistivity sensor locating between said first and second filter portions and configured to measure a resistivity of water flowing from said first stage to said second portion;



a controller configured to indicate an expiration of said replaceable deionizing filter module when said resistivity probe indicates a predefined value.

14. A plant as in claim 13, wherein said resistivity sensor is replaced as a part of said replaceable deionizing filter.

15. A water purification plant for preparing treatment fluid for use in extracorporeal blood treatment, comprising:

a replaceable deionizing filter module including a deionizing filter having first and second filter portions, configured such that water to be filtered flows first through said first portion and then through said second portion;

said first portion including separate beds of strong base anion and strong acid cation;

said second portion including a mixed bed of anion and cation;

a resistivity sensor locating between said first and second filter portions and configured to measure a resistivity of water flowing from said first portion to said second portion.

16. A plant as in claim 15, further comprising a controller configured to indicate an expiration of said replaceable deionizing filter module when said resistivity probe indicates a predefined value.

17. A fluid container device, comprising:

a sealed sterilized container with a conductivity sensor in communication with an interior of said container;

at least a first sealed connector at the end of a first line adapted for adding fluid to said container,

said first sealed connector having a second connector inline therewith;

said second connector being configured to close said first line when said second connector is disconnected from said first connector such that said first connector may be left attached to a mating external connector when said sealed sterilized container is removed from said first connector and said closed first line provides a sterile seal to said mating external connector.

18. A container as in claim 17, wherein said first connector is non-reopenable.

19. A container as in claim 17, wherein said first connector is configured such that said first line is closed automatically when said second connector is removed from said first connector.

20. A blood treatment apparatus, comprising:  
at least one controller having a data carrier writer;  
a station on said controller adapted to receive empty containers for having to hold an indicator of a date that a corresponding container was filled with purified water;  
a water purification device configured to fill a first container with purified water;  
said station being configured to write information indicating a date and time of filling of said container on said data carrier attached to said first container;  
said at least one controller having a data carrier reader;  
a blood treatment device that uses purified water from containers;  
said controller being configured to read said indicator attached to said first container and to prevent blood treatment operation or proceed therewith responsively to said information.

21. A blood treatment apparatus as in claim 20, wherein said blood treatment device is configured to perform renal replacement therapy.

22. A treatment plant for preparing purified water for medical use, comprising:  
a controller having a data carrier reader;  
a station on said controller adapted to receive filter modules for purifying water, each having a respective data carrier with a unique identifier;  
said controller being configured to read a unique identifier and compare a read unique identifier from a respective data carrier, when a module is received by said station, to at least one other identifier and to prevent a water preparation operation or proceed with a water preparation operation responsively to a result of said comparison.

23. A plant as in claim 22, wherein said at least one other identifier is included in a list of previously used filter module identifiers, whereby reuse of filter modules is prevented.

24. A treatment plant for preparing purified water for medical use, comprising:  
a water purification device;  
a controller configured to read data carriers on filter modules attachable to said water purification device, said filter modules having permanently attached data carriers carrying status information for each filter module;  
said controller being configured to read said status information of a first filter module when attached to be consumed in purifying water by said water purification device;

said controller receiving information from a sensor in said filter module indicating a contaminant breakthrough, said controller being further configured to store an updated status indicating that said filter module has been used to said data carrier;

said controller being further configured to prevent the use of said first filter module if said status indicated by the data carrier thereof indicates said first filter module was previously used.

25. A medical material preparation device, comprising:

a controller having a data carrier reader;

a station on said controller adapted to receive consumable elements required for preparing a medical material used for medical treatment, each element having a respective data carrier with a unique identifier,

said controller being configured to read a unique identifier and compare a read unique identifier from a respective data carrier, when a consumable element is received by said station, to at least one other identifier and to prevent a preparation operation or proceed with a preparation operation responsively to a result of said comparison.

26. A medical material preparation device, comprising:

a controller having a data carrier reader;

a medical material preparation component that consumes consumable elements attached to it and generates medical materials;

a station on said controller adapted to receive said consumable elements required for preparing said medical material;

each consumable element having a respective data carrier that indicates whether said particular consumable element has ever been used, either by comparing a unique identifier stored by said data carrier to a list of previously used consumable elements or by storing a programmable indicator indicating that said consumable element had been previously used;

said controller being configured to either read the identifier of the particular consumable element and compare the read unique identifier from the data carrier to a list of previously used ones or programming said data carrier to indicate previous use, automatically upon connection of said consumable element is received in said station;

said controller being configured to prevent a preparation operation or proceed with a preparation operation depending on whether said data carrier indicates that said consumable element had been previously used.

27. A device as in claim 26, wherein said controller is further configured to either store an identifier in said list or store an indication that said consumable element has been previously used upon detecting an expiration of said consumable element.

28. A device as in claim 27, wherein said consumable elements have contaminant break through detectors and said controller detects an expiration of said consumable element by detecting a break through of contaminant responsively to said detectors.

29. A medical material preparation device, comprising:  
a controller having a programmable data carrier reader;  
a medical material preparation component that consumes consumable elements attached to it and generates medical materials;

a station on said controller adapted to receive said consumable elements required for preparing said medical material;

each consumable element having a respective data carrier that stores data indicating that the particular consumable element has been previously used,

said controller being configured to store an indication in said data carrier that said consumable element has been previously used, respectively by automatically exchanging data therewith when said consumable element is connected for use in said medical material preparation component and an expiration thereof is detected;

said controller being configured to prevent a preparation operation using a preparation operation when a first consumable element is attached depending on whether said data carrier attached thereto contains an indication that said first consumable element had been previously used.

30. A medical material preparation device, comprising:  
a controller having a data carrier reader;  
a medical material preparation component that consumes consumable elements attached to it and generates medical materials;

a station on said controller adapted to receive said consumable elements required for preparing said medical material;

each consumable element having a respective data carrier that stores a unique identifier, uniquely identifying the particular consumable element,

said controller being configured to read the identifier of a first consumable element and compare the read unique identifier from the data carrier of said first consumable element, when said first consumable element is received by said station, to a stored identifier in a list of previously used consumable elements;

said controller being further configured to store said identifier in said list when an expiration of said consumable element is detected;

said controller being configured to prevent a preparation operation using said first consumable element when said read unique identifier of said first consumable element is the same as one stored in said list.

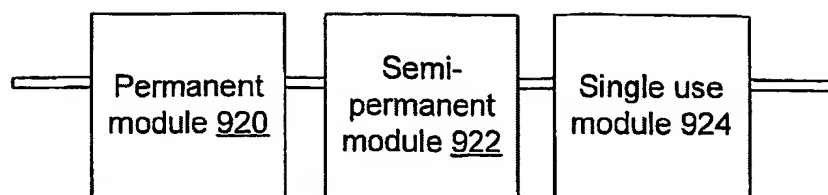
31. A medical material preparation device, comprising:

a controller having a data carrier reader;

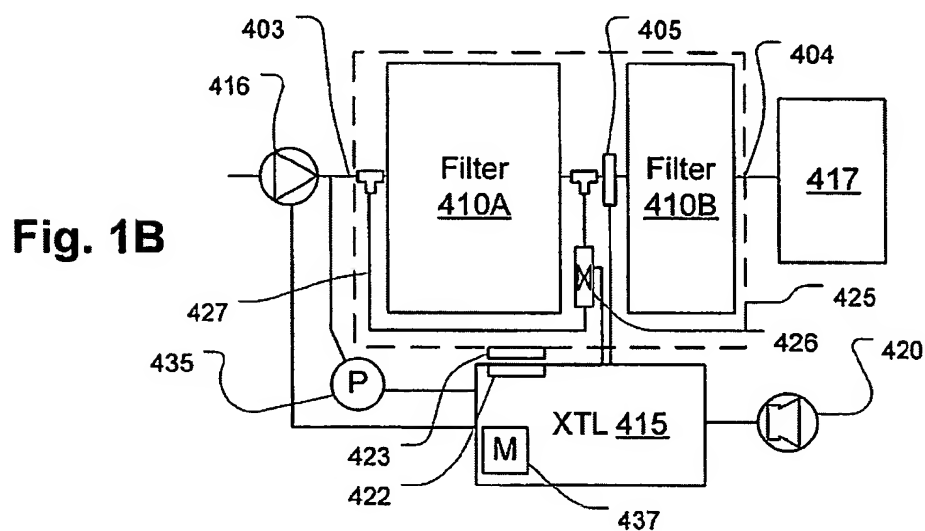
a station on said controller adapted to receive consumable elements required for preparing a medical material used for medical treatment, each element having a respective data carrier with a unique identifier,

said controller being configured to read a unique identifier and compare a read unique identifier from a respective data carrier, when a consumable element is received by said station, to at least one other identifier and to prevent a preparation operation or proceed with a preparation operation responsively to a result of said comparison;

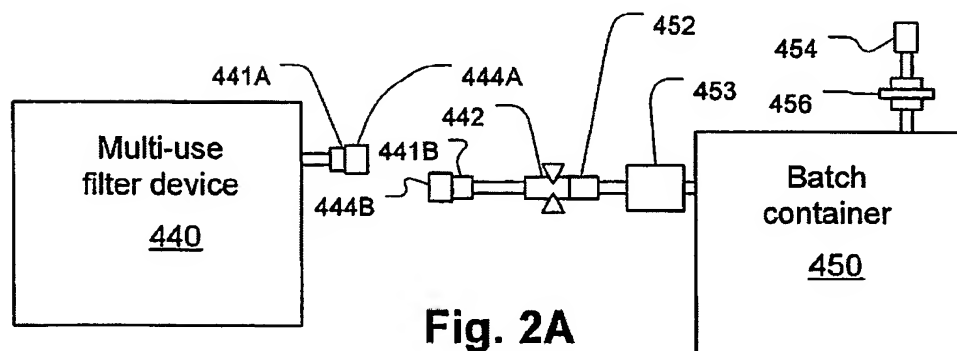
a water purification component; said medical material being purified water generated by said water purification component; wherein said consumable element includes a container adapted to receive purified water from said water purification component; said at least one other identifier is stored in a list of identifiers of previously used containers, whereby a reuse of a used container is prevented.



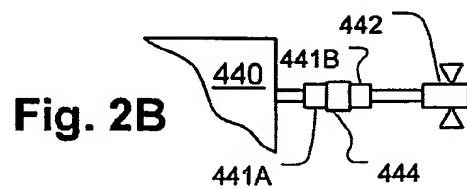
**Fig. 1A**



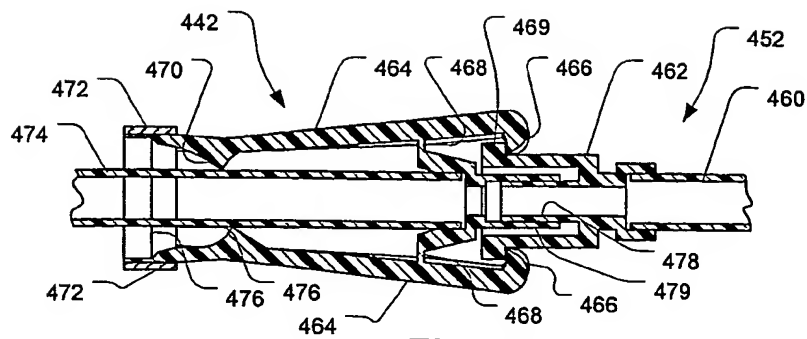
**Fig. 1B**



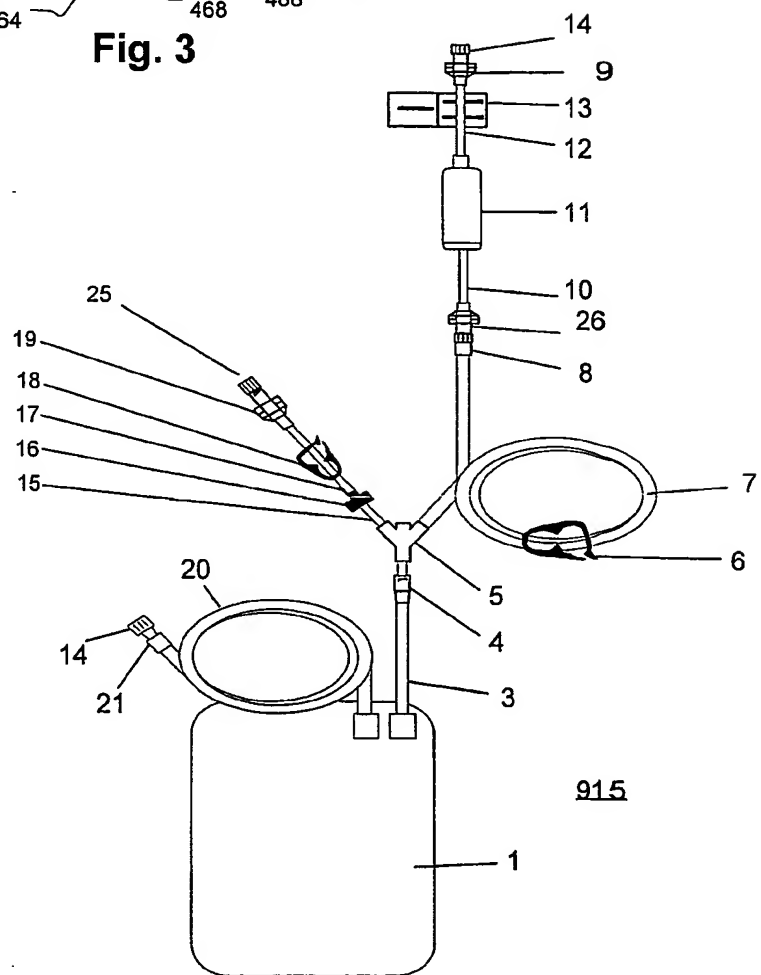
**Fig. 2A**



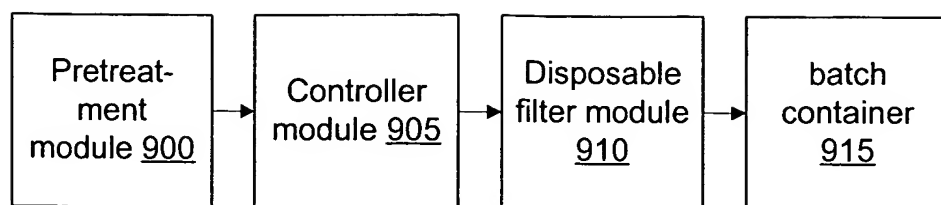
**Fig. 2B**



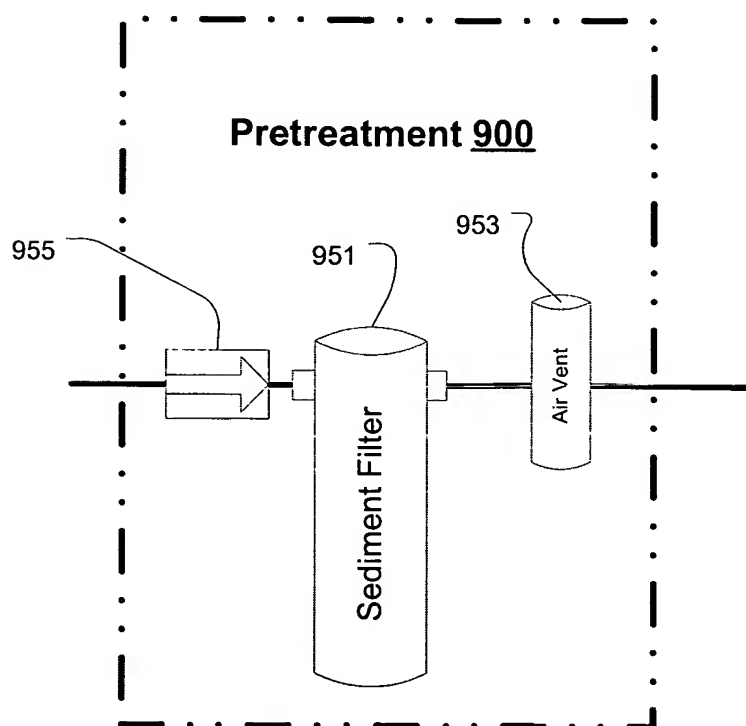
**Fig. 3**



**Fig. 4**

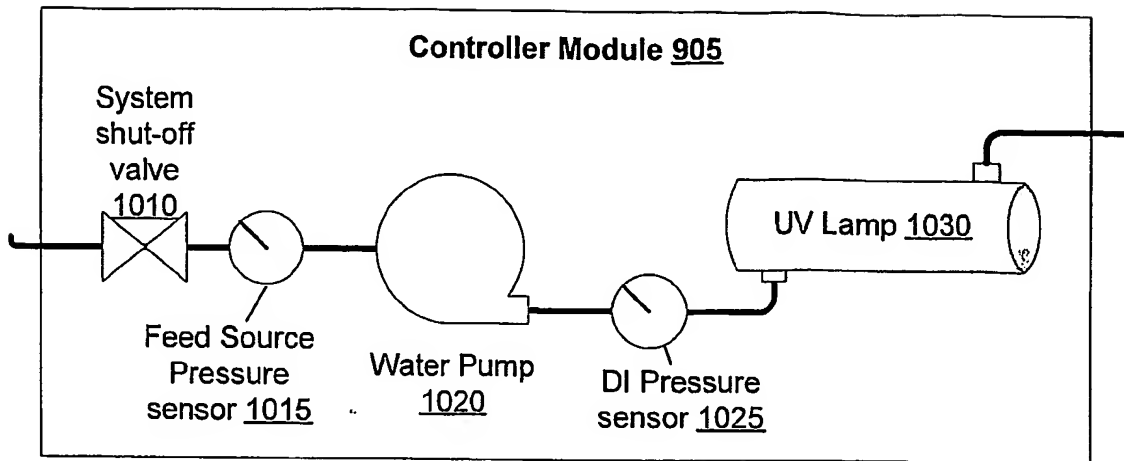


**Fig. 5**

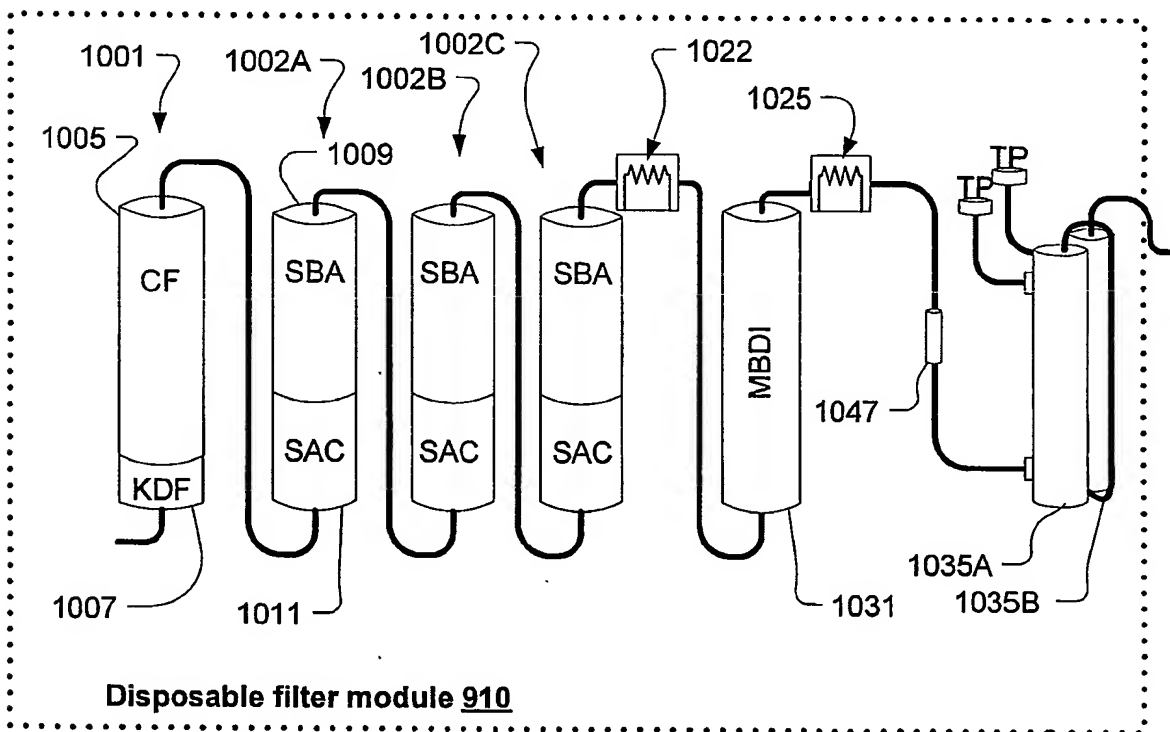


**Fig. 6**

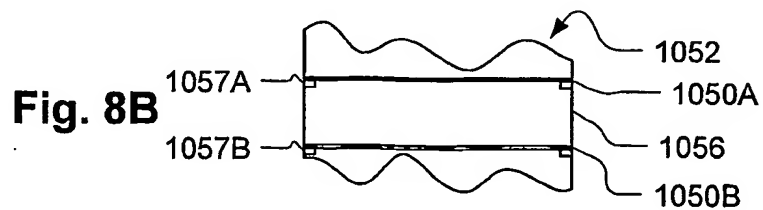




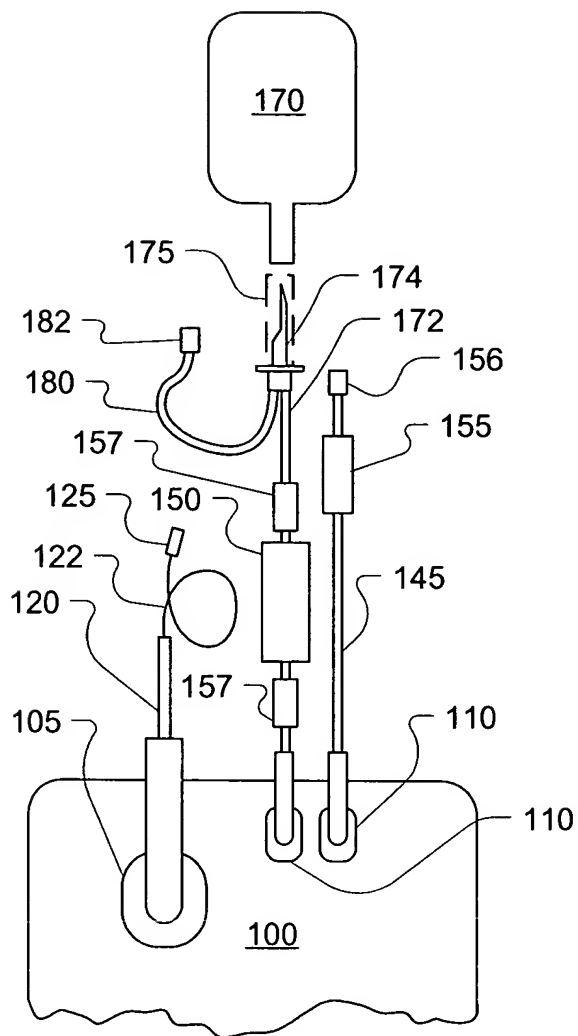
**Fig. 7**



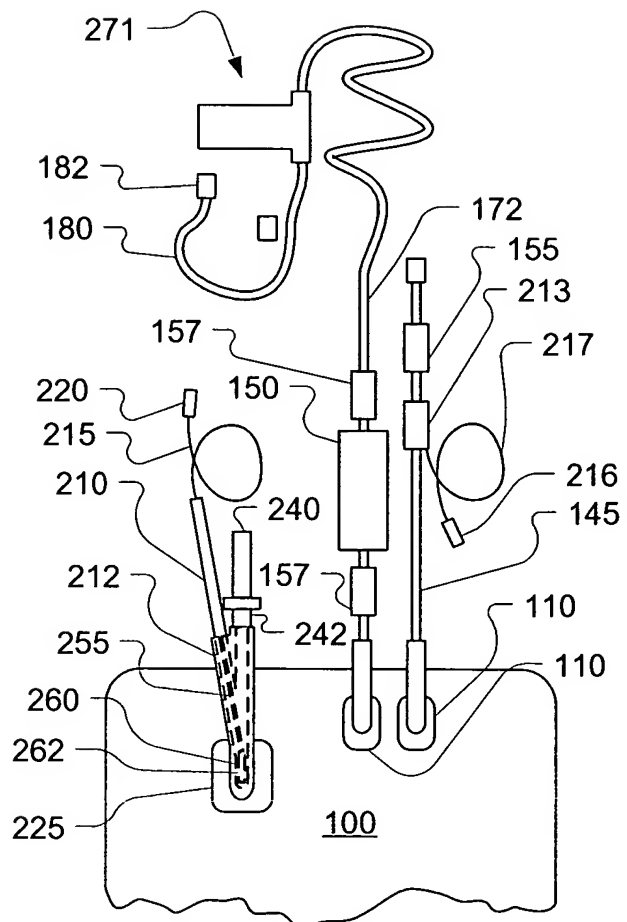
**Fig. 8A**



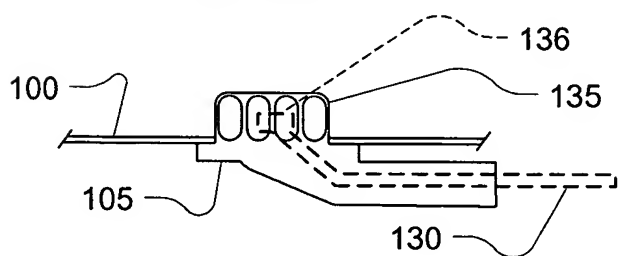
**Fig. 8B**



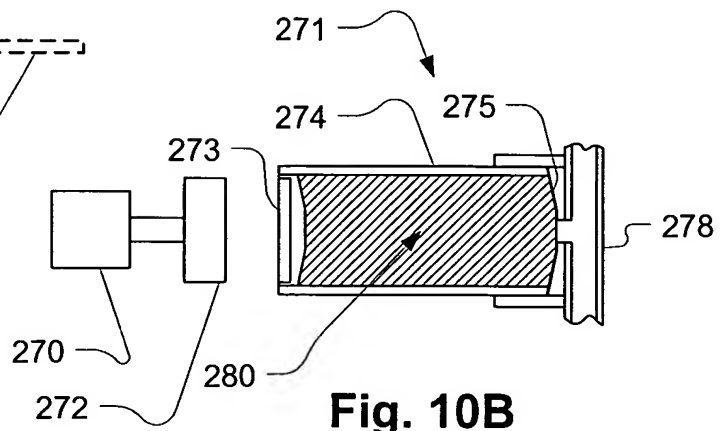
**Fig. 9A**



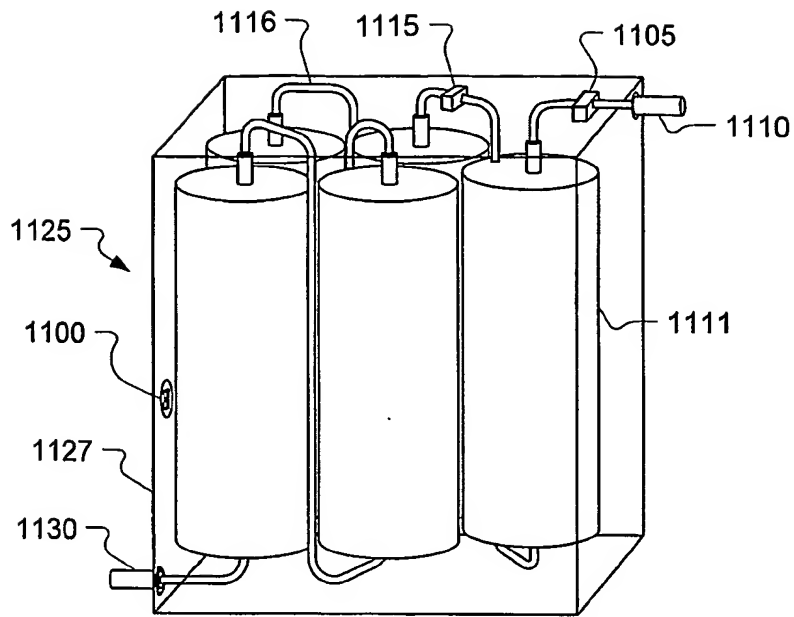
**Fig. 9B**



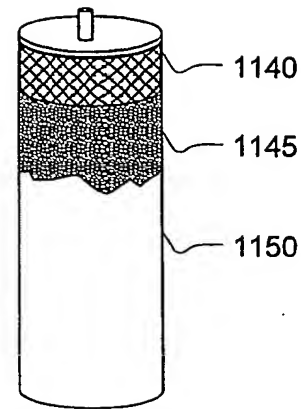
**Fig. 10A**



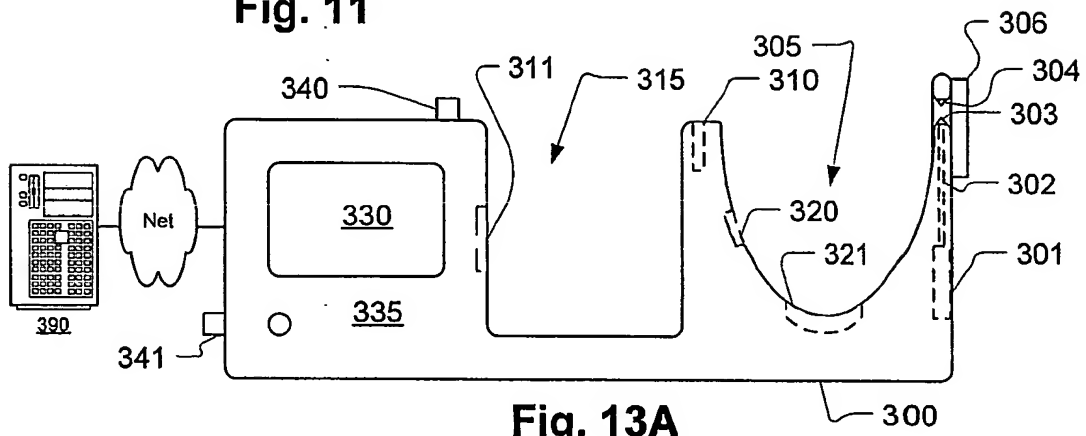
**Fig. 10B**



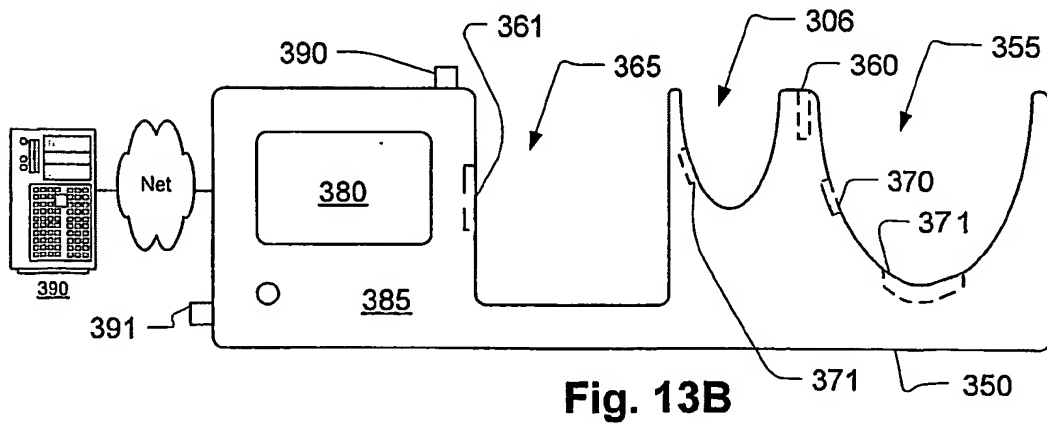
**Fig. 11**



**Fig. 12**



**Fig. 13A**



**Fig. 13B**

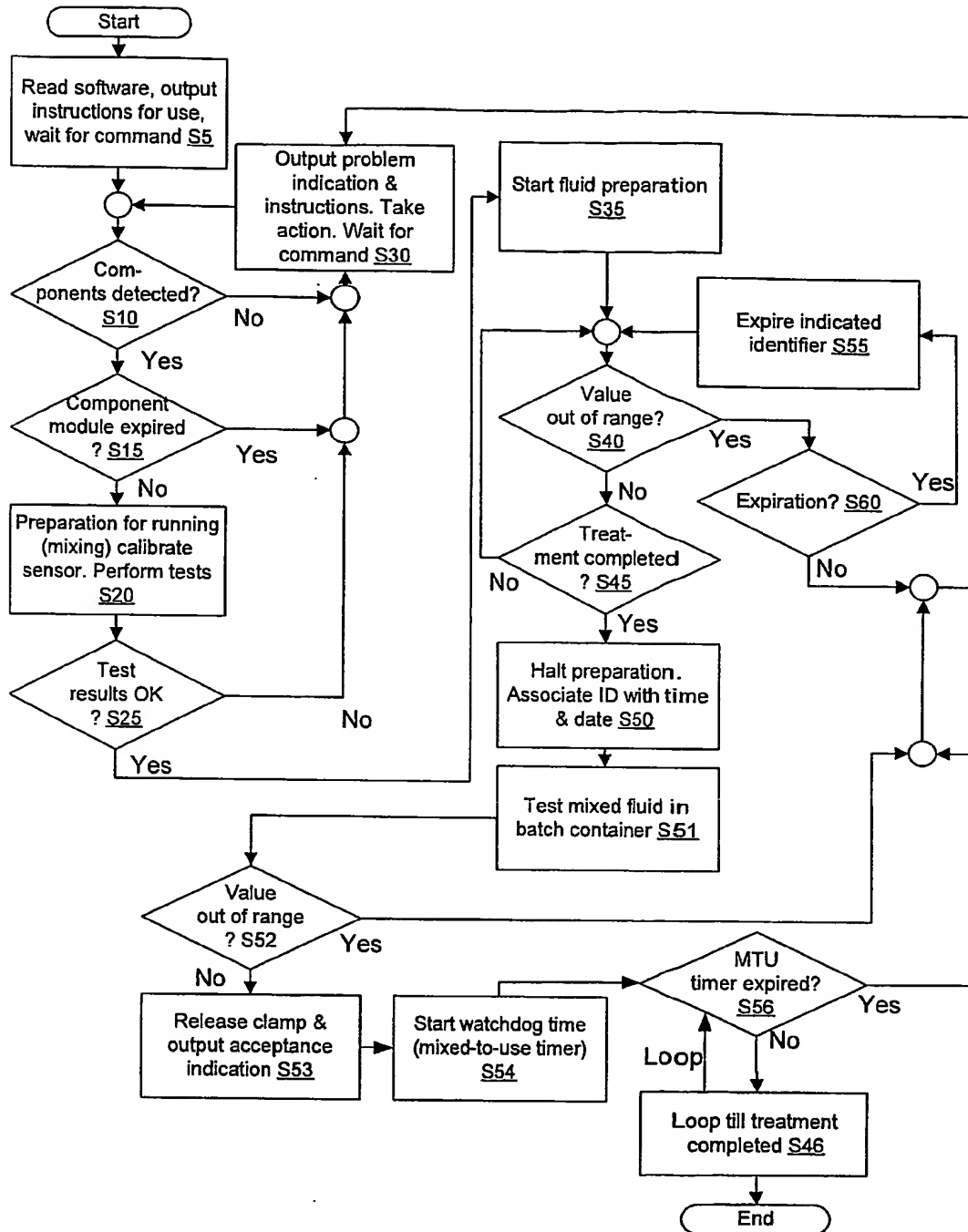
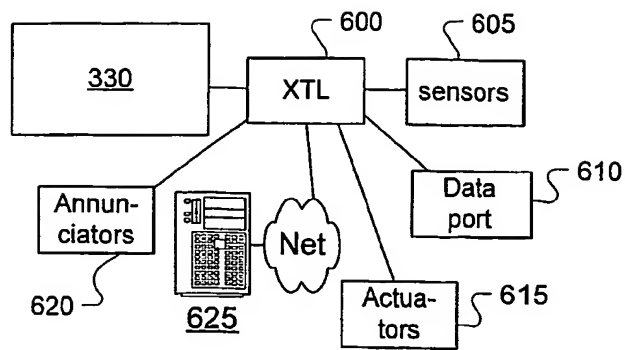
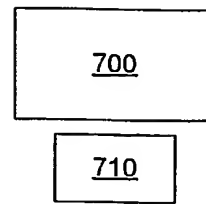


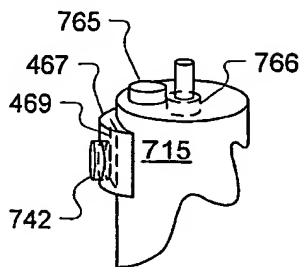
Fig. 15



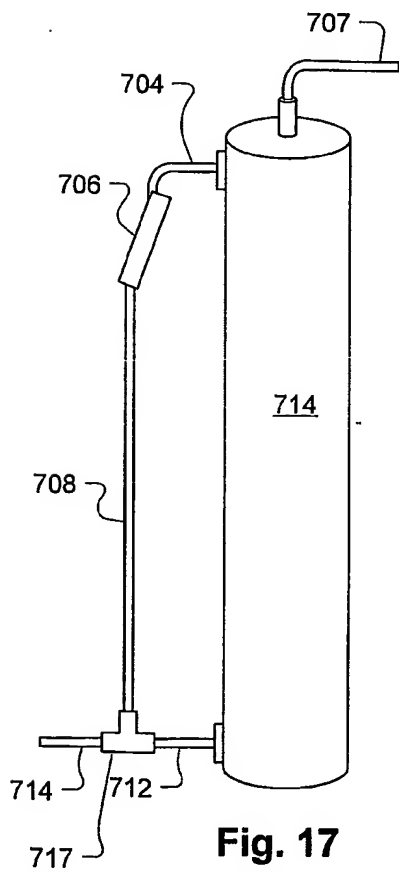
**Fig. 14**



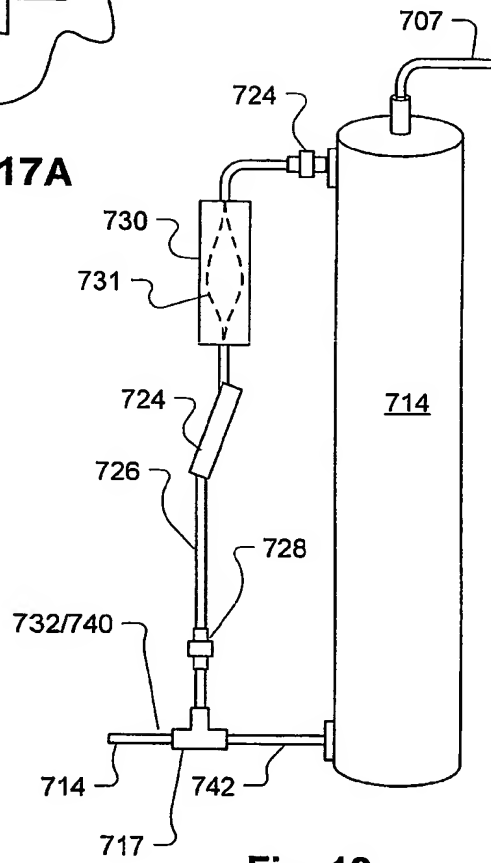
**Fig. 16**



**Fig. 17A**



**Fig. 17**



**Fig. 18**